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Effectiveness and tolerability of adjunctive perampanel in pediatric patients (aged 4–12 years) with refractory epilepsy

An observational study

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Abstract

Information on the effects of perampanel in Chinese children ≤12 years of age with refractory epilepsy is limited; thus, we conducted an observational study to assess the effectiveness, safety, and tolerability of adjunctive perampanel in this pediatric population. In this study, we reviewed the medical records of pediatric patients aged 4 to 12 years with refractory epilepsy who were admitted to Children's Hospital of Soochow University and prescribed perampanel between January 2020 and January 2021. Effectiveness of perampanel was measured by 50% responder rates, seizure-freedom rates, and retention rates for up to 48 weeks. Adverse events were monitored and recorded throughout the study. A total of 34 patients (male, n = 15) who exhibited refractory epilepsy were included in this study, and 64.71% of patients had focal-onset seizures combined with generalized epilepsy. The mean (± standard deviation) age of patients was 7.21 (± 2.12) years, with a mean (± standard deviation) age at seizure onset of 4.57 (± 2.59) years. After the addition of perampanel, the 50% responder rates at 4, 8, 12, 24, 36, and 48 weeks were 37.50% (12/32), 43.75% (14/32), 53.13% (17/32), 59.38% (19/32), 59.38% (19/32), and 62.07% (18/29). Two patients withdrew from perampanel treatment due to adverse events in the first 2 weeks. Adverse events were reported by 44.12% (15/34) of patients, and the retention rates at 36 and 48 weeks were 94.12% (32/34) and 85.29% (29/34), respectively. Overall, perampanel exhibited good effectiveness, safety, and tolerability in the treatment of pediatric patients (aged 4–12 years) with refractory epilepsy. These findings suggest that personalized treatment and better baseline seizure control may increase the responder rate and retention rate of perampanel.

Abbreviations: AEs = adverse events, AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, ASM = anti-seizure medication, EIASMs = enzyme-inducing anti-seizure medication, FIRES = febrile infection-related epilepsy syndrome, FOS = focal-onset seizures, PK = pharmacokinetic.

Keywords: adjunctive perampanel, focal-onset seizures, pediatric patients, refractory epilepsy

1. Introduction

More than a third of patients with epilepsy report frequent seizures even after treatment with standard anti-seizure medication (ASM).[1,2] In recent years, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) glutamate receptors have been found to play an important role in the pathogenesis of epilepsy.[3] Inhibition of postsynaptic AMPA receptor activity can suppress the activity of excitatory neurotransmitter glutamate, thus reducing neuronal overexcitation and emphasizing the therapeutic effect of AMPA receptor antagonists.[4]

Perampanel, a highly selective, noncompetitive AMPA receptor antagonist,[5] is a once-daily, oral ASM, and has been demonstrated as an efficacious and well-tolerated treatment of epilepsy in Phase III clinical trials and serial case studies.[6–9] In the US, perampanel is approved for the treatment of focal-onset seizures (FOS; adjunctive and monotherapy), with or without focal to bilateral tonic-clonic seizures, in patients aged ≥4 years, and as adjunctive treatment of generalized tonic-clonic seizures in patients aged ≥12 years[10]; and in China, perampanel is available as monotherapy and adjunctive treatment for FOS, with or without focal to

bilateral tonic-clonic seizures, in patients with epilepsy aged ≥4 years.[11] Comparable with adult patients, perampanel exhibits efficacy among pediatric patients aged ≥12 years[12]; however, treatment with perampanel is not uniform among pediatric patients of different races and/or ethnicities around the world. According to pharmacokinetic (PK) data, adult and pediatric patients can be prescribed the same dosage of perampanel; nonetheless, some physicians choose to prescribe perampanel based on the patient's body weight to achieve optimal clinical outcomes.[13,14] Currently, most studies on pediatric patients have focused on patients who were >12 years of age. However, dose-related toxicity has been reported in patients aged ≤2 years who received perampanel[15,16]; hence, it is important to assess the safety and tolerability of treatment protocols in younger pediatric patients with epilepsy. This study reported the effectiveness and tolerability of perampanel in pediatric patients ≤12 years of age with refractory epilepsy.

2. Materials and methods

2.1. Study design

This observational study was conducted between January 2020 and January 2021 at the Children's Hospital of Soochow University, Suzhou, China. Outpatient data and hospitalization records of patients were collected and analyzed. At baseline, patients were prescribed perampanel based on the investigator's judgment, and seizure frequency and characteristics were recorded in home diaries. Subsequent seizure data and safety outcomes were collected at 4, 8, 12, 24, 36, and 48 weeks. Patients' seizure status was assessed by clinicians at regular intervals of 28 days or less, and a telephone follow-up was conducted to collect patient data following hospital discharge.

The effectiveness of perampanel treatment was assessed by the 50% responder (hereafter referred to as responder) and seizure-freedom rate (defined as the proportion of patients with a ≥50% or 100% reduction in seizure frequency per 28 days from baseline) at 4, 8, 12, 24, 36, and 48 weeks of perampanel treatment. Safety assessments included adverse events (AEs) and AEs leading to perampanel dose adjustments. The severity of the AEs was evaluated based on approaches reported in previous studies.[6–9]

To improve the patient's compliance, parents were informed of the schedule of the next follow-up at each visit and instructed to visit the doctor in time when the child's condition worsened or the child had serious adverse reactions. In addition, the doctor would negotiate with the family over the phone to arrange the next follow-up visit for patients who did not visit their doctor on time.

2.2. Patients

Patients, aged 4 to 12 years with a diagnosis of inadequately controlled FOS based on auxiliary examination and their treating clinician's assessments, were included in this study. All patients had a diagnosis of refractory epilepsy before enrollment. Prior to perampanel treatment, patients received at least 2 ASMs at baseline and continued to experience seizures. Patients with incomplete medical records were excluded from the present analysis, and the sample size depended on the availability of eligible patients at the study site between January 2020 and January 2021.

The investigators informed the guardians of all patients before enrollment that relevant clinical data could be included for the purpose of publication. Informed consent was voluntarily provided by the patients' family members after they had the opportunity to review basic study and perampanel prescribing information. The study was approved by the Ethics Committee of Children's Hospital of Soochow University, Suzhou, China.

2.3. Medication regimen

The treatment regimen was formulated based on a dosage administration protocol that was previously reported.[13] The daily starting perampanel dose was 0.03 to 0.05 mg/kg (up to a maximum daily dose of ≤2.00 mg). Patients were up-titrated by 0.03 to 0.05 mg/kg (up to a maximum daily dose of ≤2.00 mg) every 1 to 2 weeks, until a daily maintenance dose of 0.1 to 0.2 mg/kg (up to a maximum daily dose of ≤12.00 mg) was reached. For younger patients or patients with a history of allergies, slow titration was used to reduce adverse reactions. The perampanel dosage (once daily before bedtime) was determined by the physician during subsequent study visits based on the patient's weight and changes in condition.

2.4. Statistical analysis

Statistical analyses were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC). The normality of continuous/quantitative variables was measured. Normally distributed variables were represented with arithmetic means and standard deviations, whereas variables that were not normally distributed were represented with medians and quartiles. In addition, discontinuous/quantitative variables and categorical variables were expressed as frequencies and percentages.

To identify factors that may affect treatment responses to perampanel, univariate analyses were performed based on patient's baseline characteristics. For comparisons between responders and non-responders (patients who were not defined as responders), t tests and Wilcoxon tests were used for quantitative variables (i.e., age, age at seizure onset, and time on ASMs), whereas a Fisher's exact test was used for categorical variables (i.e., sex, number of ASMs, enzyme-inducing ASMs [EIASMs], treatments other than ASMs, seizure type, epileptic syndrome or febrile infection-related epilepsy syndrome [FIRES], genetic test abnormalities, and motor and mental retardation). The differences were considered statistically significant when $P < .05$.

3. Results

3.1. Patients

In total, 34 patients met the inclusion criteria and were enrolled. Of these, 29 (85.29%) patients completed the 48-week study. Patient disposition is shown in Figure 1; the primary reason for discontinuation was AEs in 3 patients (8.82%), of whom, 2 patients withdrew during the first 2 weeks and were excluded from effectiveness analysis due to insufficient exposure to perampanel, and 1 patient withdrew after 36 weeks. All patients were included in the safety analysis, and 32 patients were included in the effectiveness analysis for up to 36 weeks of treatment with perampanel.

Patient demographics and baseline clinical characteristics are presented in Table 1. Of the 34 patients in total, 44.12% (n = 15/34) were male. The mean standard deviation age of patients at seizure onset was 4.57 (2.59) years. At baseline, patients received treatment with a range of 2 to 5 ASMs over a period of 0.13 to 10.87 years, prior to entering the study and receiving adjunctive perampanel treatment. All patients (N = 34) had focal epilepsy, of whom, 22 patients also reported generalized epilepsy. Furthermore, 9 patients suffered from epileptic syndrome or FIRES, and 4 patients had a history of brain tumor removal (n = 2) or epileptic focus (n = 2). Motor and mental retardation was observed in 19 (55.88%) patients, and 1 (2.94%) patient reported regression. The initial daily dose of perampanel ranged between 0.50 and 2.00 mg and the daily maintenance dose ranged from 0.50 to 6.00 mg.
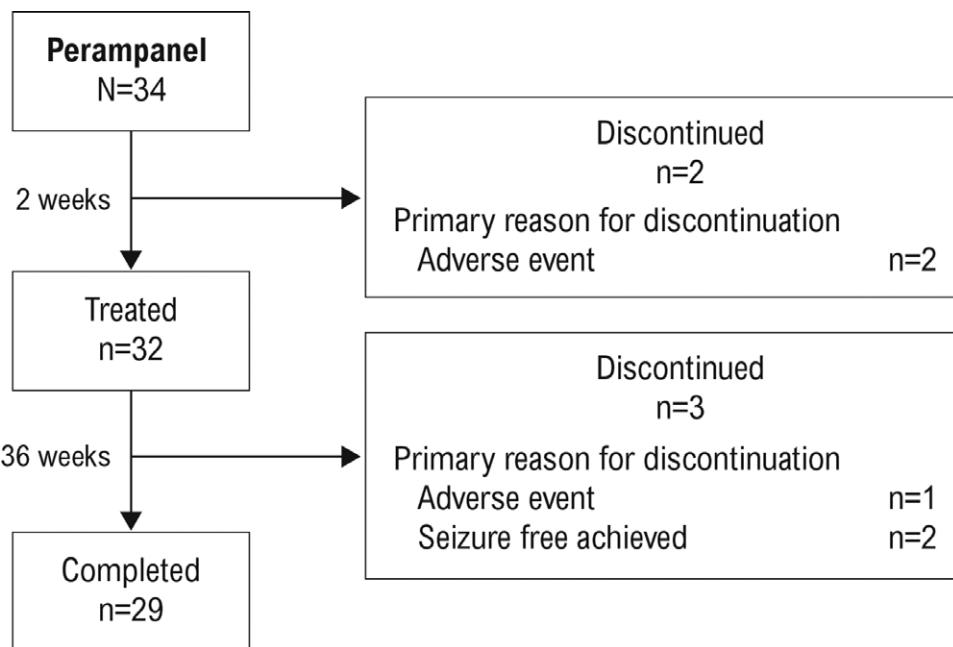
Figure 1. Patient disposition.

Patient demographics and baseline characteristics.

Characteristics	Total (N = 34)
Sex, n (%)	
Male	15 (44.12)
Age, yrs, mean ± SD	7.21 ± 2.12
Age at seizure onset, yrs, mean ± SD	4.57 ± 2.59
Number of ASMs, median (P_{25}, P_{75})	2 (2, 3)
Time on ASMs, yrs, median (P_{25}, P_{75})	2.12 (1.16, 4.06)
Seizure types, n (%)	
Focal	12 (35.29)
Combined	22 (64.71)
Epileptic syndrome, n (%)	
BECTS variant	2 (5.88)
West syndrome	1 (2.94)
Epilepsy with myoclonic absence	1 (2.94)
Frontal lobe epilepsy	2 (5.88)
Temporal lobe epilepsy	1 (2.94)
MELAS, n (%)	1 (2.94)
FIRES, n (%)	2 (5.88)
Ketogenic diet, n (%)	1 (2.94)
Genetic test abnormalities, n (%)	4 (11.76)
Motor and mental retardation, n (%)	19 (55.88)
Duration of perampanel treatment, wks, n (%)	
36	32 (94.12)
48	29 (85.29)
Initial dose of perampanel, mg/d, median (P_{25}, P_{75})	2.00 (1.00, 2.00)
Maintenance dose of perampanel, mg/d, median (P_{25}, P_{75})	3.00 (2.00, 4.00)

ASM = anti-seizure medication, BECTS = benign epilepsy with centro-temporal spikes, FIRES = febrile infection-related epilepsy syndrome, MELAS = mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes, P_{25} = first quartile, P_{75} = third quartile, SD = standard deviation.

3.2. Effectiveness

The effectiveness of perampanel treatment during the 48-week study period is shown in Figure 2. After 36 weeks of treatment with perampanel, 59.38% (n = 19/32) of patients were deemed responders; among them, 14 patients had no seizures following the initiation of perampanel treatment. Two responders who were seizure free and one non-responder discontinued perampanel treatment after 36 weeks. At Week 48, the responder rate was 62.07% (n = 18/29) and the seizure-freedom rate was 55.17% (n = 16/29). During the treatment, 5 patients tried to reduce the dose of ≥1 concomitant ASM(s) except perampanel (oxcarbazepine in 2 patients; valproate, topiramate, and nitrazepam in 1 patient each). Three patients completed the withdrawal; one experienced increases in seizure frequency, and this patient had up-titrated oxcarbazepine back to the previous maintenance dose.

To assess factors that may impact perampanel effectiveness, univariate analyses were performed to compare the clinical profile of responders with that of non-responders (Table 2). There was no statistically significant difference between responders and non-responders with respect to baseline characteristics, including sex, age at seizure onset, age at perampanel onset, duration of treatment, number of ASMs, concomitant use of EIASMs (such as phenobarbital, carbamazepine, and oxcarbazepine), therapeutic method, genetic test abnormalities, and motor or mental retardation.

3.3. Safety and tolerability

The retention rate before and at 36 weeks was sustained at 94.12% (32/34). At 48 weeks, the retention rate was 85.29% (29/34). During the 48-week study period, 44.12% (15/34) of patients experienced 1 to 3 AEs, and 3 patients discontinued perampanel due to AEs. The most common AEs were aggression (14.70%) and dizziness (8.82%) (Table 3). Perampanel was generally well tolerated by most patients, and some AEs were resolved without dose adjustment. However, 1 patient experienced a brief loss of consciousness after being up-titrated to a perampanel dosage of 5.00 mg, and this event resolved immediately after a dose reduction to 4.00 mg. An additional patient also adjusted an ASM (valproate) dosage to control their AEs successfully. None of the patients who reported AEs received any other treatments other than perampanel dose adjustment.

4. Discussion

Perampanel has been widely used for the treatment of pediatric epilepsy and has proven to be effective among patients
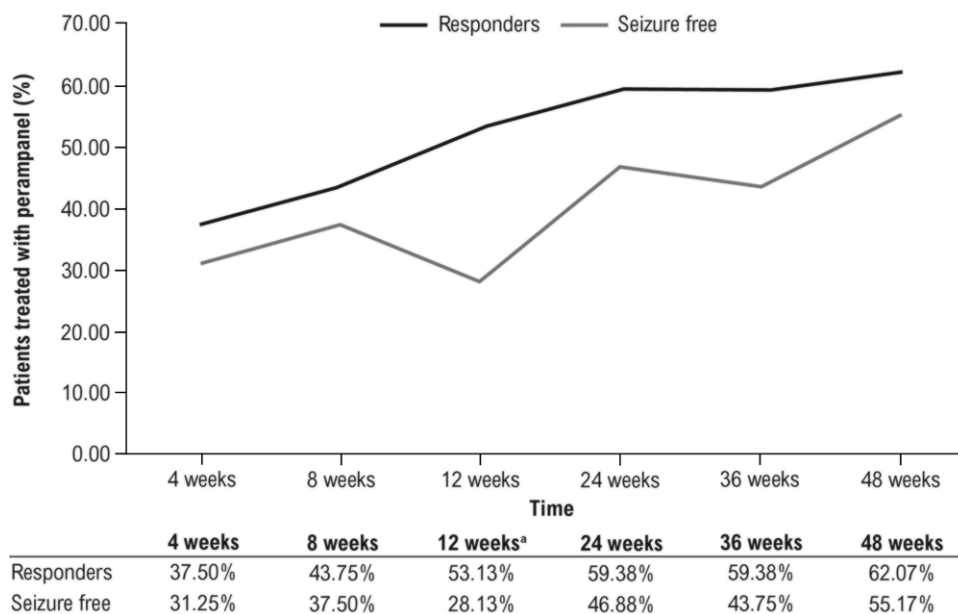
Figure 2. Effectiveness of perampanel during 48-wk follow-up. Clinical effectiveness of perampanel treatment as observed in patients at the 4-, 8-, 12-, 24-, 36-, and 48-wk evaluations. Responders were defined as patients with a ≥50% reduction in seizure frequency from baseline. [a]Three patients relapsed after being seizure free at the 12-wk evaluation.

	4 weeks	8 weeks	12 weeks[a]	24 weeks	36 weeks	48 weeks
Responders	37.50%	43.75%	53.13%	59.38%	59.38%	62.07%
Seizure free	31.25%	37.50%	28.13%	46.88%	43.75%	55.17%

Table 2

Univariate analysis of the effectiveness of perampanel.

Variable	Total (N = 32)	Responders (n = 19)	Non-responders (n = 13)	P value
Sex, n (%)				
Male	14 (43.75)	8 (42.11)	6 (46.15)	1.0000
Age, yrs, mean ± SD/median (P_{25}, P_{75})	7.17 ± 2.14	7.55 ± 2.18	6.59 ± 2.03	.2572
Age at seizure onset, yrs, mean ± SD	4.61 ± 2.50	4.51 ± 2.54	4.75 ± 2.56	.8045
Number of ASMs, median (P_{25}, P_{75})	2 (2, 3)	2 (2, 3)	3 (2, 4)	.2149
Time on ASMs, yrs, median (P_{25}, P_{75})/mean ± SD	2.12 (1.16, 3.80)	2.62 (1.16, 4.06)	2.24 ± 1.66	.3878
Enzyme-inducing ASMs, n (%)	14 (43.75)	9 (47.37)	5 (38.46)	.7249
Treatments other than ASMs, n (%)	4 (12.50)	2 (10.53)	2 (15.38)	1.0000
Seizure type, n (%)				1.0000
Focal	10 (31.25)	6 (31.58)	4 (30.77)	
Combined	22 (68.75)	13 (68.42)	9 (69.23)	
Epileptic syndrome or FIRES*, n (%)	7 (21.88)	4 (21.05)	3 (23.08)	1.0000
BECTS	2 (6.25)	1 (5.26)	1 (7.69)	
Frontal lobe epilepsy	2 (6.25)	1 (5.26)	1 (7.69)	
Temporal lobe epilepsy	1 (3.13)	1 (5.26)	——	
FIRES	2 (6.25)	1 (5.26)	1 (7.69)	
Genetic test abnormalities, n (%)	4 (12.50)	1 (5.26)	3 (23.08)	.2788
Motor and mental retardation, n (%)	19 (59.38)	11 (57.89)	8 (61.53)	1.0000

ASM = anti-seizure medication, BECTS = benign epilepsy with centro-temporal spikes, FIRES = febrile infection-related epilepsy syndrome, P_{25} = first quartile, P_{75} = third quartile, SD = standard deviation.
*Two patients (one with West syndrome and one with epilepsy with myoclonic absence) withdrew perampanel treatment in the first 2 weeks due to adverse events and were excluded from the univariate analysis.

worldwide since its regulatory approval and availability.[17–19] In September 2018, perampanel was approved to treat patients as young as 4 years of age with focal epilepsy. However, there have been few studies focused on patients ≤12 years of age, particularly patients with refractory epilepsy.

Based on previous real-world retrospective studies assessing the effectiveness of perampanel, responder rates were within a range of 17.3% to 67.9%,[9,12,18,20–23] and seizure-freedom rates ranged from 4.8% to 17.7%.[18,21,22] The data presented here

are consistent with these previously published reports and the observed responder rates in this study at 4, 8, 12, 24, 36, and 48 weeks were 37.50%, 43.75%, 53.13%, 59.37%, 59.37%, and 62.07%, respectively. During the Follow-up Period, 2 patients experienced an increase in seizure frequency and were transferred from the responder group to the non-responder group. Furthermore, 1 patient with a diagnosis of frontal lobe epilepsy experienced seizure(s) during the first 12 weeks following the initiation of perampanel treatment, and had no additional seizures

Table 3

Overview of safety outcomes among pediatric patients who received perampanel as adjunctive treatment.

	Total (N = 34)	Responders (n = 19)	Non-responders (n = 13)
All AEs, n (%)	15 (44.12)	8 (42.11)	5 (38.46)
AEs leading to perampanel dose adjustment, n (%)	4 (12.50)	2 (10.53)	——
Withdrawal	3 (8.82)	1 (5.26)	——
Somnolence	1 (2.94)	——	——
Drooling	1 (2.94)	1 (5.26)	——
Irritability	1 (2.94)	——	——
Dose reduction	1 (2.94)	1 (5.26)	——
Unconsciousness	1 (2.94)	1 (5.26)	——
AEs, n (%)			
Aggression	5 (14.70)	3 (15.79)	2 (15.38)
Dizziness	3 (8.82)	2 (10.53)	1 (7.69)
Fatigue	2 (5.88)	1 (5.26)	1 (7.69)
Weight gain	2 (5.88)	1 (5.26)	1 (7.69)
Nausea	2 (5.88)	1 (5.26)	1 (7.69)
Somnolence	2 (5.88)	1 (5.26)	1 (7.69)
Gait problems	2 (5.88)	1 (5.26)	——
Drooling	1 (2.94)	1 (5.26)	——
Unconsciousness	1 (2.94)	1 (5.26)	——
Hyperactivity	1 (2.94)	——	1 (7.69)
Depression	1 (2.94)	——	——
Irritability	1 (2.94)	——	——
Baseline ASMs received by patients with AEs, n (%)			
Topiramate	7 (20.59)	3 (15.79)	3 (23.08)
Valproate	7 (20.59)	5 (26.32)	1 (7.69)
Lacosamide	5 (14.71)	4 (21.05)	1 (7.69)
Oxcarbazepine	4 (11.76)	2 (10.53)	2 (15.38)
Levetiracetam	4 (11.76)	3 (15.79)	——
Nitrazepam	3 (8.82)	2 (10.53)	1 (7.69)

AEs = adverse events, ASM = anti-seizure medication.

during the remaining 36 weeks of the study. Patients with FIRES in the responder group experienced no apparent improvements until the evaluation at 48 weeks. Similarly, patients with epileptic syndrome or mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes did not experience any changes during the study. Six patients experienced relapse after achieving seizure freedom for up to 36 weeks. Furthermore, the responder rate was 62.07% and seizure-freedom rate was 55.17% at week 48, which are higher than what have been reported in other studies.[18,21,22]

The relatively high responder rates of this study could be due to 2 factors. First, it is possible that more frequent outpatient visits, as was included in this study, as well as more personal dose adjustments of perampanel, may have contributed to the increased seizure-freedom rates. As population PK analyses have shown that the PKs of perampanel are unrelated to age, weight, and liver function,[24] several physicians choose to prescribe pediatric patients the same dosage as prescribed in adult patients.[24–26] Although there was no considerable difference in terms of pharmacology, pediatric patients did differ from adult patients in some aspects, particularly with respect to drug sensitivity and toxicity.[16,27,28] Second, several studies have normalized dosage increases every 1 to 3 weeks under the guidance of a target dose (12 mg/day),[27,29] and some patients had dose adjustments only after 4 to 8 weeks.[2] Nevertheless, perampanel was up-titrated on a more frequent schedule for patients who had inadequately controlled seizures than the prespecified schedule (every 1–2 weeks). This approach reflects the unique epilepsy clinical care in China. Moreover, patients enrolled in this study had a lower baseline seizure frequency relative to other studies which may have contributed to the increased response rates. In a national multicenter study conducted in Korea, the enrolled participants experienced 40.7 ± 69.9 seizures per month,[18] which was higher than the baseline seizure frequency in our study (17 ± 34). In summary, a personalized medication approach

and low baseline seizure frequency may account for the higher responder rates reported in this study. Furthermore, the reasons mentioned above not only provide a reason for higher responder rates, but also the difference in seizure-freedom rates and retention rates.

Interestingly, the observed retention rates in this study were not comparable with prior studies.[18,20,22] Notably, previous studies have indicated that perampanel retention rates range from 50.0% to 85.0% and decrease significantly over the course of follow-up periods.[18,20,22] This trend was most likely related to the initial dosing and titration rate of perampanel. The patients in our study were prescribed a daily dose of 0.03 to 0.05 mg/kg as the initial dose and were up-titrated by 0.03 to 0.05 mg/kg, up to a daily maximum of 0.10 to 0.20 mg/kg, every 1 to 2 weeks. Thus, the patients in this study took longer to reach the maintenance dose. During this period, physicians had more opportunities to individualize perampanel treatment for each patient. Furthermore, lower doses of combination therapy were also available.[30] A sudden drop in seizure-freedom rates were observed at the 3-week study timepoint, which may have been due to the titration rate.

Although no statistically significant factors were identified in our study, it is important to determine the influence of other factors. For instance, EIASMs may affect the dosage of perampanel. Although concomitant use of EIASMs did not affect the response rates,[27,31] and perampanel plasma concentrations in children were still higher than the reported effective concentration (70 µg/mL), serum concentrations were still markedly lower in children taking EIASMs.[32] Additionally, some factors, including the number of ASMs ($P < .001$),[18] dysgnosia ($P = .003$),[21] age at seizure onset ($P = .005$ and $P = .048$, respectively),[22,27] and duration of treatment ($P = .013$),[18] were proven to have statistical significance in prior studies.

AEs to perampanel have been reported in 22.6% to 60.6% of patients, varying through different studies.[17,18,23] The most

common AEs among pediatric patients included somnolence (15.3%–24.6%), dizziness (15.5%–20.4%), and aggressive behavior (2.8%–22.7%).[2,12,33] Most AEs, such as dizziness, were transient and resolved with a small reduction in dosage.[34] Compared with the overall population, aggressive behavior, somnolence, and fatigue were more common in pediatric patients.[33] In patients aged <12 years, somnolence was the most common treatment-emergent adverse events, and potentially the most frequently reported treatment-emergent adverse events.[23] In terms of weight gain, few studies have reported the impact of perampanel treatment on weight change in pediatric patients. However, serum concentration of perampanel and mental retardation may increase the likelihood of weight gain in patients.[35] In our study, 2 patients (prescribed 2.00 and 4.00 mg/kg, respectively; both with motor and mental retardation) had unusually large appetites and a tendency towards obesity. Since the serum concentration of perampanel was not regularly monitored, this study was not powered to assess the relationship between serum concentration and weight gain. In addition, 1 patient with no previous AEs experienced a brief loss of consciousness at an increased perampanel dosage of 5.00 mg. Although this resolved soon after reducing perampanel dose, the patient developed an ill-tempered manner. According to a previous study, the number of baseline ASMs was inversely related to the results of the Epworth Sleepiness Scale assessment, and associated with the severity of daytime sleepiness.[36] Given this patient concomitantly received 3 ASMs, it is more likely that the somnolence of this patient was dose-related. Another AE, uncommon in previous studies, was irritability; the patient suffered from allergies and developed a rash on her face after taking perampanel.

Furthermore, perampanel may improve sleep quality and reduce the risk of strokes.[36,37] In a study investigating sleep quality, researchers observed that 9 patients with sleep disorders reported improved sleep quality and long-term cessation of hypnotics after perampanel treatment.[36] In fact, following 3 months of perampanel treatment, there was an overall improvement in sleep quality and daytime sleepiness was also reduced after 6 months.[36] An enhanced heart rate variability and vagal tone was shown in the perampanel group compared with the control groups[37]; as such, perampanel may be a suitable ASM for patients with sleep disorders and cardiovascular risk. This observational study provides valuable information on the effects of perampanel in pediatric patients. The sample size of this study depended on the availability of eligible patients at the study site between January 2020 and January 2021, and no statistical analysis was performed to estimate the study size. As such, the interpretation of these data may be limited due to the small number of patients that were recruited in this study. Additionally, as this study was open label by design, inherent bias of investigators and patients' perception of unblind treatment, as well as limited patient diversity, were inevitable and may have an impact on the clinical outcomes and implications of these results. Finally, the generalizability of study results may be restricted due to the lack of patient diversity, given that this was a single-center study.

5. Conclusion

Treatment with adjunctive perampanel was effective and generally well tolerated in patients aged 4 to 12 years with refractory epilepsy. Moreover, for some epileptic syndromes, perampanel presented similar effectiveness and tolerability. Personalized perampanel dosing and baseline seizure control may be associated with improved effectiveness and retention rate of perampanel in the treatment of refractory epilepsy. For patients with sleep disturbance or underlying cardiovascular risk, perampanel may have potential advantages as a treatment of refractory epilepsy.

Author contributions

Ji-Hong Tang and Si-Jia Chu contributed to the conception and design of the study. Ji-Hong Tang and Yan Li contributed to patient recruitment and enrollment. Si-Jia Chu, Yan Li, and Ji-Hong Tang contributed to the acquisition of the data. Si-Jia Chu conducted the analysis of the data. All authors were involved in data interpretation, reviewing, and approval of the manuscript, and the decision to submit the article for publication.

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References

[1] Santamarina E, Bertol V, Garayoa V, et al. Efficacy and tolerability of perampanel as a first add-on therapy with different anti-seizure drugs. Seizure. 2020;83:48–56.
[2] Kim SY, Kim WJ, Kim H, et al. Clinical experience with perampanel in intractable focal epilepsy over 12 months of follow-up. J Epilepsy Res. 2018;8:61–5.
[3] Wright SK, Wilson MA, Walsh R, et al. Abolishing spontaneous epileptiform activity in human brain tissue through AMPA receptor inhibition. Ann Clin Transl Neurol. 2020;7:883–90.
[4] Leo A, Giovannini G, Russo E, et al. The role of AMPA receptors and their antagonists in status epilepticus. Epilepsia. 2018;59:1098–108.
[5] Di Bonaventura C, Labate A, Maschio M, et al. AMPA receptors and perampanel behind selected epilepsies: current evidence and future perspectives. Expert Opin Pharmacother. 2017;18:1751–64.
[6] Tsai JJ, Wu T, Leung H, et al. Perampanel, an AMPA receptor antagonist: from clinical research to practice in clinical settings. Acta Neurol Scand. 2018;137:378–91.
[7] Rohracher A, Zimmermann G, Villanueva V, et al. Perampanel in routine clinical use across Europe: pooled, multicenter, observational data. Epilepsia. 2018;59:1727–39.
[8] Liguori C, Izzi F, Manfredi N, et al. Efficacy and tolerability of perampanel and levetiracetam as first add-on therapy in patients with epilepsy: a retrospective single center study. Epilepsy Behav. 2018;80:173–6.
[9] Krauss GL, Perucca E, Kwan P, et al. Final safety, tolerability, and seizure outcomes in patients with focal epilepsy treated with adjunctive perampanel for up to 4 years in an open-label extension of phase III randomized trials: study 307. Epilepsia. 2018;59:866–76.
[10] Food and Drug Administration (FDA). FYCOMPA® Prescribing Information. 2021. Available at: https://www.fycompa.com/-/media/Files/Fycompa/Fycompa_Prescribing_Information.pdf [accessed September 23, 2022].
[11] Eisai Co., Ltd. Anti-epileptic drug Fycompa® approved in China as monotherapy for partial-onset seizures and pediatric indication for partial-onset seizures. 2021. Available at: https://www.eisai.com/news/2021/news202166.html [accessed September 23, 2022].
[12] Rosenfeld W, Conry J, Lagae L, et al. Efficacy and safety of perampanel in adolescent patients with drug-resistant partial seizures in three double-blind, placebo-controlled, phase III randomized clinical studies and a combined extension study. Eur J Paediatr Neurol. 2015;19:435–45.

[13] Yoshitomi S, Takahashi Y, Yamaguchi T, et al. Efficacy and tolerability of perampanel in pediatric patients with Dravet syndrome. Epilepsy Res. 2019;154:34–8.

[14] Wachiropathum P, Nabangchang C, Likasitthananon N, et al. Efficacy of oral perampanel in status epilepticus and acute repetitive seizures in children at a tertiary care hospital in Thailand. Epilepsy Behav. 2021;118:107964.

[15] Winkler GA, Minns AB, Kreshak AA. Severe perampanel toxicity in a pediatric patient with prolonged symptoms. J Emerg Med. 2021;61:e99–e102.

[16] Dean D, Passalacqua KD, Dolcourt B. Truncal ataxia and prolonged coma in an exploratory pediatric perampanel ingestion. J Med Toxicol. 2021;17:309–11.

[17] Macrohon B, Janette Resurreccion-De La Calzada J, Sanchez-Gan B. Clinical experience on the use of perampanel in epilepsy among child neurologists in the Philippines. Brain Dev. 2021;43:411–8.

[18] Hwang SK, Lee YJ, Nam SO, et al. Real-life effectiveness and tolerability of perampanel in pediatric patients aged 4 years or older with epilepsy: a Korean national multicenter study. J Clin Neurol. 2020;16:53–9.

[19] Piña-Garza JE, Rosenfeld W, Saeki K, et al. Efficacy and safety of adjunctive perampanel in adolescent patients with epilepsy: post hoc analysis of six randomized studies. Epilepsy Behav. 2020;104(Pt A):106876.

[20] Nishida T, Lee SK, Inoue Y, et al. Adjunctive perampanel in partial-onset seizures: Asia-Pacific, randomized phase III study. Acta Neurol Scand. 2018;137:392–9.

[21] Ishikawa N, Tateishi Y, Tani H, et al. Clinical profiles associated with serum perampanel concentrations in children with refractory epilepsy. Epilepsy Behav. 2019;94:82–6.

[22] De Liso P, Vigevano F, Specchio N, et al. Effectiveness and tolerability of perampanel in children and adolescents with refractory epilepsies-An Italian observational multicenter study. Epilepsy Res. 2016;127:93–100.

[23] Ikemoto S, Hamano S, Hirata Y, et al. Efficacy and serum concentrations of perampanel for treatment of drug-resistant epilepsy in children, adolescents, and young adults: comparison of patients younger and older than 12 years. Seizure. 2019;73:75–8.

[24] Renfroe JB, Mintz M, Davis R, et al. Adjunctive perampanel oral suspension in pediatric patients from ≥2 to <12 years of age with epilepsy: pharmacokinetics, safety, tolerability, and efficacy. J Child Neurol. 2019;34:284–94.

[25] Swiderska N, Tan HJ, Rajai A, et al. Effectiveness and tolerability of perampanel in children, adolescents and young adults with refractory epilepsy: a UK national multicentre study. Seizure. 2017;52:63–70.

[26] Wheless J, Wechsler RT, Lancman M, et al. Perampanel in real-world clinical care of patients with epilepsy: interim analysis of a phase IV study. Epilepsia Open. 2021;6:79–89.

[27] Yun Y, Kim D, Lee YJ, et al. Efficacy and tolerability of adjunctive perampanel treatment in children under 12 years of age with refractory epilepsy. Korean J Pediatr. 2019;62:269–73.

[28] Culjat M, Huizenga MN, Forcelli PA. Age-dependent anticonvulsant actions of perampanel and brivaracetam in the methyl-6,7-dimethoxy-4-ethyl-beta-carboline-3-carboxylate (DMCM) model of seizures in developing rats. Pharmacol Rep. 2021;73:296–302.

[29] Lagae L, Villanueva V, Meador KJ, et al. Adjunctive perampanel in adolescents with inadequately controlled partial-onset seizures: a randomized study evaluating behavior, efficacy, and safety. Epilepsia. 2016;57:1120–9.

[30] Zhang R, Qiao S, Fang X, et al. Efficacy of perampanel as adjunctive therapy in chinese patients with focal-onset seizures: an observational, prospective study. Front Neurol. 2021;12:731566.

[31] Lin KL, Lin JJ, Chou ML, et al. Efficacy and tolerability of perampanel in children and adolescents with pharmacoresistant epilepsy: the first real-world evaluation in Asian pediatric neurology clinics. Epilepsy Behav. 2018;85:188–94.

[32] Gaudio E, Gienapp AJ, Wheless J. Perampanel pharmacokinetics in children: correlation of dose with serum concentrations. J Child Neurol. 2019;34:427–31.

[33] Trinka E, Steinhoff BJ, Nikanorova M, et al. Perampanel for focal epilepsy: insights from early clinical experience. Acta Neurol Scand. 2016;133:160–72.

[34] Rohracher A, Kalss G, Leitinger M, et al. Two-year real-world experience with perampanel in patients with refractory focal epilepsy: Austrian data. Ther Adv Neurol Disord. 2016;9:445–53.

[35] Iwaki H, Jin K, Sugawara N, et al. Perampanel-induced weight gain depends on level of intellectual disability and its serum concentration. Epilepsy Res. 2019;152:1–6.

[36] Toledo M, Gonzalez-Cuevas M, Miro-Llado J, et al. Sleep quality and daytime sleepiness in patients treated with adjunctive perampanel for focal seizures. Epilepsy Behav. 2016;63:57–62.

[37] Dono F, Evangelista G, Consoli S, et al. Perampanel enhances the cardiovagal tone and heart rate variability (HRV) in patients with drug-resistant temporal lobe epilepsy. Seizure. 2022;99:16–23.